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(54) Title: METHODS AND COMPOSITIONS FOR TREATING ERECTILE DYSFUNCTION

(57) Abstract

The present invention provides for a method for the treatment of erectile dysfunction in a male or female human subject in need of such treatment comprising administration of a therapeutically effective amount of an agonist of the melanocortin receptor in combination with a therapeutically effective amount of a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist. Further, the present invention provides for pharmaceutical compositions useful in the methods of the present invention, as well as a method of manufacture of a medicament useful for treating erectile dysfunction.

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TITLE OF THE INVENTION

METHODS AND COMPOSITIONS FOR TREATING ERECTILE DYSFUNCTION

FIELD OF THE INVENTION

5 The present invention provides for novel methods for the treatment of
erectile dysfunction comprising a drug combination. More particularly, the drug
combination of the present invention comprises an agonist of the melanocortin
receptor with a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-
adrenergic receptor antagonist. The present invention also provides for
10 pharmaceutical compositions comprising such drug combinations useful in the
methods to treat erectile dysfunction. Moreover, the present invention provides for a
method of manufacture of a medicament useful in the treatment of erectile
dysfunction.

15 BACKGROUND OF THE INVENTION

Erectile dysfunction denotes the medical condition of inability to
achieve penile erection sufficient for successful sexual intercourse. The term
"impotence" is oftentimes employed to describe this prevalent condition.
Approximately 140 million men worldwide, and, according to a National Institutes of
20 Health study, about 30 million American men suffer from impotency or erectile
dysfunction. It has been estimated that the latter number could rise to 47 million men
by the year 2000. Erectile dysfunction can arise from either organic or psychogenic
causes, with about 20% of such cases being purely psychogenic in origin. Erectile
dysfunction increases from 40% at age 40, to 67% at age 75, with over 75% occurring
25 in men over the age of 50. In spite of the frequent occurrence of this condition, only a
small number of patients have received treatment because existing treatment
alternatives, such as injection therapies, penile prosthesis implantation, and vacuum
pumps, have been uniformly disagreeable [for a discussion, see "ABC of sexual health
- erectile dysfunction," Brit. Med. J. 318: 387-390 (1999)]. Only more recently have
30 more viable treatment modalities become available, in particular orally active agents,
such as sildenafil citrate, marketed by Pfizer under the brand name of Viagra®.
Sildenafil is a selective inhibitor of type V phosphodiesterase (PDE-V), a cyclic-
GMP-specific phosphodiesterase isozyme [see R.B. Moreland et al., "Sildenafil: A
Novel Inhibitor of Phosphodiesterase Type 5 in Human Corpus Cavernosum Smooth
35 Muscle Cells," Life Sci., 62: 309-318 (1998)]. Prior to the introduction of Viagra®

on the market, less than 10% of patients suffering from erectile dysfunction received treatment. Sildenafil is also being evaluated in the clinic for the treatment of female sexual dysfunction.

The regulatory approval of Viagra® for the oral treatment of erectile dysfunction has invigorated efforts to discover even more effective methods to treat erectile dysfunction. Several additional selective PDE-V inhibitors are in clinical trials. UK-114542 is a sildenafil backup from Pfizer with supposedly improved properties. IC-351 (ICOS Corp.) is claimed to have greater selectivity for PDE-V over PDE-VI than sildenafil. Other PDE-V inhibitors include M-54033 and M-54018 from Mochida Pharmaceutical Co. and E-4010 from Eisai Co., Ltd.

Other pharmacological approaches to the treatment of erectile dysfunction have been described [see, e.g., "Latest Findings on the Diagnosis and Treatment of Erectile Dysfunction," Drug News & Perspectives, 9: 572-575 (1996); "Oral Pharmacotherapy in Erectile Dysfunction," Current Opinion in Urology, 7: 349-353 (1997)]. A product under clinical development by Zonagen is an oral formulation of the alpha-adrenoceptor antagonist phentolamine mesylate under the brand name of Vasomax®. Vasomax® is also being evaluated for the treatment of female sexual dysfunction.

Drugs to treat erectile dysfunction act either peripherally or centrally. They are also classified according to whether they "initiate" a sexual response or "facilitate" a sexual response to prior stimulation [for a discussion, see "A Therapeutic Taxonomy of Treatments for Erectile Dysfunction: An Evolutionary Imperative," Int. J. Impotence Res., 9: 115-121 (1997)]. While sildenafil and phentolamine act peripherally and are considered to be "enhancers" or "facilitators" of the sexual response to erotic stimulation, sildenafil appears to be efficacious in both mild organic and psychogenic erectile dysfunction. Sildenafil has an onset of action of 30-60 minutes after an oral dose with the effect lasting about 4 hours, whereas phentolamine requires 5-30 minutes for onset with a duration of 2 hours. Although sildenafil is effective in a majority of patients, it takes a relatively long time for the compound to show the desired effects. The faster-acting phentolamine appears to be less effective and to have a shorter duration of action than sildenafil. Oral sildenafil is effective in about 70% of men who take it, whereas an adequate response with phentolamine is observed in only 35-40% of patients. Both compounds require erotic stimulation for efficacy. Since sildenafil indirectly increases blood flow in the systemic circulation by enhancing the smooth muscle relaxation effects of nitric

oxide, it is contraindicated for patients with unstable heart conditions or cardiovascular disease, in particular patients taking nitrates, such as nitroglycerin, to treat angina. Other adverse effects associated with the clinical use of sildenafil include headache, flushing, dyspepsia, and "abnormal vision," the latter the result of inhibition of the type VI phosphodiesterase isozyme (PDE-VI), a cyclic-GMP-specific phosphodiesterase that is concentrated in the retina. "Abnormal vision" is defined as a mild and transient "bluish" tinge to vision, but also an increased sensitivity to light or blurred vision. Moreover, since some patients have developed a tolerance to prior phosphodiesterase inhibitors, sildenafil may prove to have a similar outcome in some percentage of patients when used over a long period of time.

Synthetic melanocortin receptor agonists (melanotropic peptides) have been found to initiate erections in men with psychogenic erectile dysfunction [See H. Wessells *et al.*, "Synthetic Melanotropic Peptide Initiates Erections in Men With Psychogenic Erectile Dysfunction: Double-Blind, Placebo Controlled Crossover Study," *J. Urol.*, 160: 389-393 (1998); Fifteenth American Peptide Symposium, June 14-19, 1997 (Nashville TN)]. Activation of melanocortin receptors of the brain appears to cause normal stimulation of sexual arousal. In the above study, the centrally acting α -melanocyte-stimulating hormone analog, melanotan-II (MT-II), exhibited a 75% response rate, similar to results obtained with apomorphine, when injected intramuscularly or subcutaneously to males with psychogenic erectile dysfunction. MT-II is a synthetic cyclic heptapeptide, Ac-Nle-c[Asp-His-DPhe-Arg-Trp-Lys]-NH₂, which contains the 4-10 melanocortin receptor binding region common to α -MSH and adrenocorticotropin, but with a lactam bridge. MT-II (also referred to as PT-14) (Erectide®) is presently in clinical development by Palatin Technologies, Inc. and TheraTech, Inc. as a non-penile subcutaneous injection formulation. An oral transmucosal delivery system for the drug is also being developed. It is considered to be an "initiator" of the sexual response. The time to onset of erection with this drug is relatively short (10-20 minutes) with a duration of action approximately 2.5 hours. Adverse reactions observed with MT-II include nausea, flushing, loss of appetite, stretching, and yawning.

Adverse effects associated with MT-II may be the result of the lack of selectivity of the compound for a particular melanocortin receptor subtype. To date, five melanocortin receptor subtypes have been cloned. Evidence has been presented suggesting that the erectogenic properties of melanocortin agonists are mediated via binding to the MC-4R subtype. Whereas MC-3R is expressed in the brain, gut, and

placenta, the MC-4R subtype is uniquely expressed in the brain, and inactivation has been found to cause obesity.

Because of the unresolved deficiencies of the various pharmacological agents discussed above, there is a continuing need in the medical arts for improved methods and compositions to treat individuals suffering from psychogenic and/or organic erectile dysfunction. Such methods should have wider applicability, enhanced convenience and ease of compliance, short onset of action, reasonably long duration of action, and minimal side effects with few contraindications, as compared to agents now available.

It is therefore an object of the present invention to provide methods of treating erectile dysfunction which comprise the administration to a human subject in need thereof a centrally-acting agent that "initiates" an erectogenic response in combination with another centrally-acting agent or a peripherally-acting agent that "facilitates" or "enhances" the response to erotic stimulation. The human subject may be either male or female.

It is another object of the present invention to provide pharmaceutical compositions comprising the combination that are useful in the methods of the present invention.

It is still a further object of the present invention to provide a method of manufacture of a medicament useful in the treatment of erectile dysfunction.

SUMMARY OF THE INVENTION

The present invention provides for methods of treating erectile dysfunction in a human subject in need of such treatment comprising administration of a therapeutically effective amount of an agonist of the melanocortin receptor in combination with a therapeutically effective amount of a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist. Further, the present invention provides for pharmaceutical compositions useful in the methods of the present invention, as well as a method of manufacture of a medicament useful to treat erectile dysfunction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is concerned with the combination of an agonist of the melanocortin receptor with a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist for the treatment of erectile dysfunction in

a male or female human subject. This particular combination produces unexpectedly superior pharmacokinetic and pharmacodynamic results in the treatment of male or female erectile dysfunction. Thus, it is an object of the instant invention to describe the combination of the two drugs in the treatment of erectile dysfunction. In addition, it is an object of the instant invention to describe preferred embodiments within each category of compounds which are used as elements in the instant combination. It is a further object of this invention to describe compositions containing each of the compounds for use in the treatment of erectile dysfunction. It is a still further object of this invention to describe a method of manufacture of a medicament containing the present drug combination which is useful for the treatment of erectile dysfunction. Further objects will become apparent from a reading of the following description.

The instant combination for the treatment of erectile dysfunction contains as a first element an agonist of the melanocortin receptor. Representative agonists of the melanocortin receptor are disclosed in the following publications, which are incorporated by reference herein in their entirety:

- (1) M. E. Hadley et al., "Discovery and Development of Novel Melanogenic Drugs," in Integration of Pharmaceutical Discovery and Development: Case Studies, edited by Borchardt et al., Plenum Press, New York, 1998;
- (2) R.T. Dorr, et al., "Evaluation of Melanotan-II, A Superpotent Cyclic Melanotropic Peptide in a Pilot Phase-I Clinical Study," Life Sci., 58: 1777-1784 (1996); and
- (3) R.A.H. Adan, "Identification of Antagonists for Melanocortin MC3, MC4, and MC5 Receptors," European J. Pharmacol., 269: 331-337 (1994).

Compositions and methods for the treatment of psychogenic erectile dysfunction comprising melanotropic peptides are disclosed in U.S. Patent No. 5,576,290 and CA 2,158,425, which are incorporated by reference herein in their entirety.

In the instant combination for the treatment of erectile dysfunction, the first element of the combination is an agonist of the melanocortin receptor. In one embodiment of the combination of the present invention, the agonist of the melanocortin receptor is melanotan-II (MT-II).

In another embodiment of the combination of the present invention, the agonist of the melanocortin receptor is selective for the MC-4R subtype. Selective MC-4R agonists have been described, and reference is made to the following disclosures, which are incorporated by reference herein in their entirety:

(1) C. Haskell-Luevano, et al., "Discovery of Prototype Peptidomimetic Agonists at the Human Melanocortin Receptors MC1R and MC4R," J. Med. Chem., 40: 2133-2139 (1997); and

5 (2) H.B. Schioth, et al., "Discovery of Novel Melanocortin-4 Receptor Selective MSH Analogues," Brit. J. Pharmacol., 124: 75-82 (1998).

In the instant combination for the treatment of erectile dysfunction, the second element of the combination is composed of either a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist. In a further embodiment of the combination of the present invention, the second element of the combination is a cyclic-GMP-specific phosphodiesterase inhibitor selective for the type V phosphodiesterase isozyme (PDE-V). Representative PDE-V inhibitors are disclosed in the patent and scientific literature. The Pfizer pyrazolo[4,3-d]pyrimidin-7-one PDE-V inhibitors are disclosed in WO 94/28902; WO 96/16644; WO 96/16657; EP 0,702,555; EP 0,463,756; CA 2,163,446; and U.S. Patent No. 15 5,250,534; all of which are incorporated by reference herein in their entirety. Sildenafil is the generic name for 1-[4-ethoxy-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulfonyl]-4-methyl-piperazine. For a discussion of its efficacy in the treatment of male erectile dysfunction, reference is made to I. Goldstein et al., N. Engl. J. Med., 338: 1397-1404 (1998) and M. Boolell et al., "Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase 20 inhibitor for the treatment of penile erectile dysfunction," Int. J. Impotence Res., 8: 47-52 (1996).

The ICOS Corp. tetracyclic PDE-V inhibitors are disclosed in WO 95/19978; WO 97/03675; and WO 97/19978; all of which are incorporated by reference herein in their entirety. IC-351 represents (6R, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1': 6,1]pyrido[3,4-b]indole-1,4-dione and is disclosed in WO 97/03675 for the treatment of impotence.

The Mochida Pharmaceutical Co. pyridocarbazole series of PDE-V inhibitors, of which M-54018 and M-54033 are members, is disclosed in WO 30 97/45427, which is incorporated by reference herein in its entirety. Other structural classes of PDE-V inhibitors are disclosed in WO 98/16224 (E. Merck GmbH), WO 99/02161 (Forssmann), WO 98/07430 (Eisai), and JP 8225541 (Eisai); all of which are incorporated by reference herein in their entirety.

In a class of this embodiment of the present invention, the combination 35 for the treatment of erectile dysfunction comprises an agonist of the melanocortin

receptor and a PDE-V inhibitor selected from the group consisting of sildenafil citrate, IC-351, M-54018, and M-54033. In a subclass of this class of the present invention, the agonist of the melanocortin receptor is MT-II. In another subclass of this class of the present invention, the combination of the present invention comprises a selective
5 agonist of the melanocortin-4 receptor and a PDE-V inhibitor selected from the group consisting of sildenafil citrate, IC-351, M-54018, and M-54033. An especially preferred combination is a selective agonist of the melanocortin-4 receptor (MC-4R) and sildenafil citrate.

In another embodiment of the combination of the present invention, the
10 second element of the combination is an alpha-adrenergic receptor antagonist. In a class of this embodiment of the present invention, the alpha-adrenergic receptor antagonist is selective for the alpha-2 receptor subtype. In a subclass of this class of the present invention, the alpha-2 receptor antagonist is yohimbine or delquamine. The efficacy of yohimbine in the treatment of psychogenic erectile dysfunction is
15 reported in Lancet, pp. 42-43 (1987). Delquamine is an alpha adrenoreceptor antagonist, with a greater affinity for the alpha-2 receptor subtype [see A. Morales et al., "Oral and topical treatment of erectile dysfunction," Urol. Clin. North Am., 22: 879-885 (1995)].

In another subclass of this class of the present invention, the alpha-2
20 receptor antagonist is an arylquinolizine derivative disclosed in U.S. Patent Nos. 4,824,849 and 4,710,504, both of which are incorporated by reference herein in their entirety. In a subclass of this subclass of the present invention, the alpha-2 receptor antagonist is the benzofuroquinolizine analog, MK-912, disclosed in U.S. Patent No. 4,824,849. MK-912 represents 1',3'-dimethylspiro(1,3,4,5',6,6',7,12b-octahydro-2H-
25 benzo[b]-furo[2,3-a]quinolizine)-2,4'-pyrimidin-2'-one and is a potent, orally active agent with a pharmacologic profile consistent with alpha-2 antagonism [see D.J. Pettibone, et al., "Pharmacological profile of a new potent and specific alpha2-adrenoceptor antagonist, L-657,743," Naunyn-Schmiederberg's Arch. Pharmacol., 336: 169-175 (1987)]. The effect of the drug on penile erections in healthy male
30 volunteers was observed by B.J. Gertz et al. and reported in Clin. Pharmacol. Ther., 46: 566-575 (1989). An especially preferred combination is a selective agonist of the melanocortin-4 receptor (MC-4R) and MK-912.

The instant combination of an agonist of the melanocortin receptor and
a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor
35 antagonist is useful in the therapeutic treatment of erectile dysfunction. Although the

methods and compositions comprising drug combinations of the present invention are envisaged primarily for the treatment of male erectile dysfunction, they may also be useful for the treatment of female sexual dysfunction, including orgasmic dysfunction related to clitoral disturbances.

5 The combination of an agonist of the melanocortin receptor and a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist provides an unexpectedly superior effect in the treatment of erectile dysfunction. The combination provides for effective treatment of either psychogenic or organic erectile dysfunction in a greater percentage of the affected population than
10 either element of the combination separately. The combination provides for a shorter onset of action and longer duration of action than either element of the combination separately. The combination also has fewer side effects and contraindications than either member of the combination separately.

For use in medicine, the salts of the compounds of this invention refer
15 to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable
20 organic or inorganic acid. Representative salts include the following:

Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycolylarsanilate, Hexylresorcinate, Hydrabamine,
25 Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isothionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Mucate, Napsylate, Nitrate, N-methylglucamine ammonium salt, Oleate, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Salicylate, Stearate, Sulfate, Subacetate,
30 Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide and Valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts.

The compounds of the present invention may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. Therefore, where a compound is chiral, the separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of erectile dysfunction with the compound specifically disclosed as an element of the combination or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

In the combination of the present invention, the agonist of the melanocortin receptor may be administered separately or in conjunction with the cyclic-GMP-specific phosphodiesterase inhibitor or the alpha-adrenergic receptor antagonist. In addition, the administration of one element of the combination of the present invention may be prior to, concurrent to, or subsequent to the administration of the other element of the combination.

The elements of the combination of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), buccal, nasal, vaginal, rectal, sublingual, or

topical (e.g., ocular eyedrop) routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

5 The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the
10 pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in the combination in an amount sufficient to produce the desired pharmacologic effect upon
15 the process or condition of erectile dysfunction..

 The pharmaceutical compositions containing the active ingredient suitable for oral administration may be in the form of discrete units such as hard or soft capsules, tablets, troches or lozenges, each containing a predetermined amount of the active ingredient; in the form of a dispersible powder or granules; in the form of a
20 solution or a suspension in an aqueous liquid or non-aqueous liquid; in the form of syrups or elixirs; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening
25 agents, flavoring agents, coloring agents and preserving agents in order to provide a pharmaceutically elegant and palatable preparation.

 Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compounds are admixed with at least one inert pharmaceutically acceptable carrier such as sucrose,
30 lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

 Tablets containing the active ingredient in admixture with non-toxic
35 pharmaceutically acceptable excipients may also be manufactured by known methods.

The excipients used may be for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents, such as corn starch or alginic acid; (3) binding agents such as starch, gelatin or acacia; and (4) lubricating agents such as magnesium stearate, stearic acid or talc.

5 The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and
10 4,265,874 to form osmotic therapeutic tablets for controlled release.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an
15 oil medium, for example peanut oil, liquid paraffin, or olive oil.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and
20 suspending agents, and sweetening, flavoring, and perfuming agents.

Aqueous suspensions normally contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients may be

- 25 1) suspending agents such as sodium carboxymethyl-cellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia;
- (2) dispersing or wetting agents which may be
- 30 (a) a naturally-occurring phosphatide such as lecithin,
(b) a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate,
(c) a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethylenoxycetanol,

- (d) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or
- (e) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

5 The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents, such as sucrose or
10 saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening
15 agents and flavoring agents may be added to provide a palatable oral preparation. These compositions may be prepared by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a
20 dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, those sweetening, flavoring and coloring agents described above may also be present.

The pharmaceutical compositions of the invention may also be in the
25 form of oil-in-water emulsions. The oily phase may be a vegetable oil such as olive oil or arachis oils, or a mineral oil such as liquid paraffin or a mixture thereof. Suitable emulsifying agents may be (1) naturally-occurring gums such as gum acacia and gum tragacanth, (2) naturally-occurring phosphatides such as soybean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for
30 example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also
35 contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension or solution. The suspension may be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile
5 injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane-diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this
10 purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspension, or emulsions.
15 Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing
20 agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. The combination of this invention may also be administered in the form of suppositories for rectal administration. This composition
25 can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols. Compositions for buccal, nasal or sublingual administration are also prepared with standard excipients well known in the art.

30 For topical administration the combination of this invention may be formulated in liquid or semi-liquid preparations such as liniments, lotions, applications; oil-in-water or water-in-oil emulsions such as creams, ointments, jellies or pastes, including tooth-pastes; or solutions or suspensions such as drops, and the like.

The dosage of the active ingredients in the compositions of this invention may be varied. However, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration and on the duration of the treatment. Dosage ranges in the combination for the melanocortin receptor agonist and cyclic-GMP-specific phosphodiesterase inhibitor or alpha-adrenergic receptor antagonist are approximately one tenth to one times the clinically effective ranges required to induce the desired erectogenic effect, respectively when the compounds are used singly. Generally, dosage levels of the melanocortin receptor agonist of between about 0.001 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 250 and 500 milligrams of each of the active ingredients for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of each of the active ingredients, preferably, from about 1 mg to about 100 mg of each of the active ingredients. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Dosage levels of the cyclic-GMP-specific phosphodiesterase inhibitor or alpha-adrenergic receptor antagonist of between about 0.001 to 50 mg/kg of body weight daily, preferably about 0.005 to about 25 mg/kg per day, and more preferably about 0.01 to about 10 mg/kg per day are administered to a patient to obtain effective treatment of erectile dysfunction.

An especially preferred combination is that wherein the agonist of the melanocortin receptor is selective for the MC-4R subtype, the cyclic-GMP-specific phosphodiesterase inhibitor is the PDE-V inhibitor sildenafil citrate or IC-351, and the alpha-adrenergic receptor antagonist is the alpha-2 antagonist MK-912. In this especially preferred combination, dosage levels of each component are as noted above; however, it is even more preferred that the agonist of the MC-4R subtype be administered at a dosage rate of about 0.01 to about 10 mg/kg/day, especially about 0.05 to about 5.0 mg/kg/day, and more particularly about 0.1 to about 5 mg/kg/day, and that the PDE-V inhibitor, sildenafil citrate or IC-351, or the alpha-2 antagonist MK-912 be administered at a dosage level of about 0.001 to about 20 mg/kg/day,

especially about 0.005 to about 10 mg/kg/day, and more particularly about 0.01 to about 5 mg/kg/day.

More particularly illustrating the invention is a pharmaceutical composition comprising any of the compounds described above and a pharmaceutically acceptable carrier. Another example of the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. Another illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

The test procedures used to measure the efficacy of the combination of the present invention to treat erectile dysfunction are described below in the following examples. These examples are not intended to be limitations on the scope of the instant invention in any way, and they should not be so construed.

EXAMPLE 1

Binding Assay.

The membrane binding assay is used to identify competitive inhibitors of ^{125}I - α -NDP-MSH binding to cloned human melanocortin receptors expressed in L- or CHO- cells.

Cell lines expressing melanocortin receptors are grown in T-180 flasks containing selective medium of the composition: 1 L Dulbecco's modified Eagles Medium (DMEM) with 4.5 g L-glucose, 25 mM Hepes, without sodium pyruvate, (Gibco/BRL); 100 ml 10% heat-inactivated fetal bovine serum (Sigma); 10 ml 10,000 unit/ml penicillin & 10,000 $\mu\text{g}/\text{ml}$ streptomycin (Gibco/BRL); 10 ml 200 mM L-glutamine (Gibco/BRL); 1 mg/ml Geneticin (G418) (Gibco/BRL). The cells are grown at 37°C with CO₂ and humidity control until the desired cell density and cell number are obtained.

The medium is poured off and 10 mls/monolayer of enzyme-free dissociation media (Specialty Media Inc.) is added. The cells are incubated at 37°C for 10 minutes or until cells slough off when flask is banged against hand.

5 The cells are harvested into 200 ml centrifuge tubes and spun at 1000 rpm, 4°C, for 10 min. The supernatant is discarded and the cells are resuspended in 5 mls/monolayer membrane preparation buffer having the composition: 10 mM Tris pH 7.2-7.4; 4 µg/ml Leupeptin (Sigma); 10 µM Phosphoramidon (Boehringer Mannheim); 40 µg/ml Bacitracin (Sigma); 5 µg/ml Aprotinin (Sigma); 10 mM Pefabloc (Boehringer Mannheim). The cells are homogenized with motor-driven
10 dounce (Talboy setting 40), using 10 strokes and the homogenate centrifuged at 6,000 rpm, 4°C, for 15 minutes.

The pellets are resuspended in 0.2 mls/monolayer membrane prep buffer and aliquots are placed in tubes (500-1000 µl/tube) and quick frozen in liquid nitrogen and then stored at -80°C.

15 Test compounds or unlabelled NDP-α-MSH is added to 100 µL of membrane binding buffer to a final concentration of 1 µM. The membrane binding buffer has the composition: 50 mM Tris pH 7.2; 2 mM CaCl₂; 1 mM MgCl₂; 5 mM KCl; 0.2% BSA; 4 µg/ml Leupeptin (SIGMA); 10 µM Phosphoramidon (Boehringer Mannheim); 40 µg/ml Bacitracin (SIGMA); 5 µg/ml Aprotinin (SIGMA); and 10
20 mM Pefabloc (Boehringer Mannheim). One hundred µl of membrane binding buffer containing 10-40 µg membrane protein is added, followed by 100 µM ¹²⁵I-NDP-α-MSH to final concentration of 100 pM. The resulting mixture is vortexed briefly and incubated for 90-120 min at room temperature while shaking.

The mixture is filtered with a Packard Microplate 196 filter apparatus
25 using Packard Unifilter 96-well GF/C filter with 0.1% polyethyleneimine (Sigma). The filter is washed (5 times with a total of 10 ml per well) with room temperature of filter wash having the composition: 50mM Tris-HCl pH 7.2 and 20 mM NaCl. The filter is dried, and the bottom sealed and 50 µl of Packard Microscint-20 is added to each well. The top is sealed and the radioactivity quantitated in a Packard Topcount
30 Microplate Scintillation counter.

EXAMPLE 2

Functional assay.

Functional cell based assays are developed to discriminate melanocortin agonists and antagonists.

Cells (for example, CHO- or L-cells or other eukaryotic cells) expressing a human melanocortin receptor [see e.g. Yang-YK; Ollmann-MM; Wilson-BD; Dickinson-C; Yamada-T; Barsh-GS; Gantz-I; Mol. Endocrinol., 11: 274-80 (1997)] are dissociated from tissue culture flasks by rinsing with Ca and Mg free phosphate buffered saline (14190-136, Life Technologies, Gaithersburg, MD) and detached following 5 minutes incubation at 37°C with enzyme free dissociation buffer (S-014-B, Specialty Media, Lavellette, NJ). Cells are collected by centrifugation and resuspended in Earle's Balanced Salt Solution (14015-069, Life Technologies, Gaithersburg, MD) with additions of 10 mM HEPES pH 7.5, 5 mM MgCl₂, 1 mM glutamine and 1 mg/ml bovine serum albumin. Cells are counted and diluted to 1 to 5 x 10⁶/ml. The phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine is added to cells to 0.6 mM.

Test compounds are diluted in dimethylsulfoxide (DMSO) (10⁻⁵ to 10⁻¹⁰ M) and 0.1 volume of compound solution is added to 0.9 volumes of cell suspension; the final DMSO concentration is 1%. After room temperature incubation for 45 min., cells are lysed by incubation at 100°C for 5 min. to release accumulated cAMP.

cAMP is measured in an aliquot of the cell lysate with the Amersham (Arlington Heights, IL) cAMP detection assay (RPA556). The amount of cAMP production which results from an unknown compound is compared to that amount of cAMP produced in response to alpha-MSH which is defined as a 100% agonist. The EC₅₀ is defined as the compound concentration which results in half maximal stimulation, when compared to its own maximal level of stimulation.

Antagonist assay: Antagonist activity is defined as the ability of a compound to block cAMP production in response to alpha-MSH. Solution of test compounds and suspension of receptor containing cells are prepared and mixed as described above; the mixture is incubated for 15 min., and an EC₅₀ dose (approximately 10 nM alpha-MSH) is added to the cells. The assay is terminated at 45 min. and cAMP quantitated as above. Percent inhibition is determined by comparing the amount of cAMP produced in the presence to that produced in the absence of test compound.

EXAMPLE 3

Rat Ex Copula Assay.

Sexually mature male Caesarian Derived Sprague Dawley (CD) rats (over 60 days old) are used with the suspensory ligament surgically removed to prevent retraction of the penis back into the penile sheath during the *ex copula* evaluations. Animals receive food and water *ad lib* and are kept on a normal light/dark cycle. Studies are conducted during the light cycle.

a) Conditioning to Supine Restraint for Ex Copula Reflex Tests.

This conditioning takes ~ 4 days. Day 1, the animals are placed in a darkened restrainer and left for 15 - 30 minutes. Day 2, the animals are restrained in a supine position in the restrainer for 15 - 30 minutes. Day 3, the animals are restrained in the supine position with the penile sheath retracted for 15 - 30 minutes. Day 4, the animals are restrained in the supine position with the penile sheath retracted until penile responses are observed. Some animals require additional days of conditioning before they are completely acclimated to the procedures; non-responders are removed from further evaluation. After any handling or evaluation, animals are given a treat to ensure positive reinforcement.

b) Ex Copula Reflex Tests. Rats are gently restrained in a supine position with their anterior torso placed inside a cylinder of adequate size to allow for normal head and paw grooming. For a 400-500 gram rat, the diameter of the cylinder is approximately 8 cm. The lower torso and hind limbs are restrained with a non-adhesive material (vetrap). An additional piece of vetrap with a hole in it, through which the glans penis will be passed, is fastened over the animal to maintain the preputial sheath in a retracted position. Penile responses will be observed, typically termed *ex copula* genital reflex tests. Typically, a series of penile erections will occur spontaneously within a few minutes after sheath retraction. The types of normal reflexogenic erectile responses include elongation, engorgement, cup and flip. An elongation is classified as an extension of the penile body. Engorgement is a dilation of the glans penis. A cup is defined as an intense erection where the distal margin of the glans penis momentarily flares open to form a cup. A flip is a dorsiflexion of the penile body.

Baseline and or vehicle evaluations are conducted to determine how and if an animal will respond. Some animals have a long duration until the first response while others are non-responders altogether. During this baseline evaluation

latency to first response, number and type of responses are recorded. The testing time frame is 15 minutes after the first response.

After a minimum of 1 day between evaluations, these same animals are administered the test compound or combination at 20 mg/kg and evaluated for penile reflexes. All evaluations are videotaped and scored later. Data are collected and analyzed using paired 2 tailed t-tests to compare baseline and/or vehicle evaluations to drug- or combination- treated evaluations for individual animals. Groups of a minimum of 4 animals are utilized to reduce variability.

Positive reference controls are included in each study to assure the validity of the study. Animals can be dosed by a number of routes of administration depending on the nature of the study to be performed. The routes of administration include intravenous (IV), intraperitoneal (IP), subcutaneous (SC) and intracerebral ventricular (ICV).

15

EXAMPLE 4

Models of Female Sexual Dysfunction

Rodent assays relevant to female sexual receptivity include the behavioral model of lordosis and direct observations of copulatory activity. There is also a urethrogenital reflex model in anesthetized spinally transected rats for measuring orgasm in both male and female rats. These and other established animal models of female sexual dysfunction are described in McKenna KE et al, A Model For The Study Of Sexual Function In Anesthetized Male And Female Rats, Am. J. Physiol. (Regulatory Integrative Comp. Physiol 30): R1276-R1285, 1991; McKenna KE et al, Modulation By Peripheral Serotonin Of The Threshold For Sexual Reflexes In Female Rats, Pharm. Bioch. Behav., 40:151-156, 1991; and Takahashi LK et al, Dual Estradiol Action In The Diencephalon And The Regulation Of Sociosexual Behavior In Female Golden Hamsters, Brain Res., 359:194-207, 1985.

30

EXAMPLE 5

As a specific embodiment of an oral composition of a combination of the present invention, 5 mg of a melanocortin agonist and 10 mg of a type V phosphodiesterase (PDE-V) inhibitor are formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

35

EXAMPLE 6

As another specific embodiment of an oral composition of a combination of the present invention, 2.5 mg of a melanocortin agonist and 5 mg of an alpha-2 receptor antagonist are formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the patient being treated for erectile dysfunction. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound or combination selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A method for the treatment of erectile dysfunction which comprises administering to a human subject in need of such treatment an effective amount of an agonist of the melanocortin receptor in combination with an effective amount of a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist.
2. The method of Claim 1 wherein said human subject is male.
3. The method of Claim 1 wherein said human subject is female.
4. The method of Claim 1 wherein the agonist of the melanocortin receptor is melanotan-II (MT-II).
5. The method of Claim 1 wherein the agonist of the melanocortin receptor agonist is selective for the melanocortin-4 receptor (MC-4R) subtype.
6. The method of Claim 1 wherein the inhibitor of the cyclic-GMP-specific phosphodiesterase is an inhibitor of the type V phosphodiesterase (PDE-V) isozyme.
7. The method of Claim 6 wherein the inhibitor of PDE-V is selected from the group consisting of:
 - a) sildenafil citrate,
 - b) IC-351,
 - c) M-54033,
 - d) M-54018, and
 - e) E-4010.
8. The method of Claim 7 wherein the inhibitor of PDE-V is sildenafil citrate.
9. The method of Claim 8 wherein the agonist for the melanocortin receptor is selective for the melanocortin-4 receptor subtype.

10. The method of Claim 1 wherein the alpha-adrenergic receptor antagonist is selective for the alpha-2 receptor subtype.

5 11. The method of Claim 10 wherein the alpha-2 receptor antagonist is yohimbine, delquamine, or MK-912.

12. The method of Claim 11 wherein the alpha-2 receptor antagonist is MK-912.

10 13. The method of Claim 12 wherein the agonist for the melanocortin receptor is selective for the melanocortin-4 receptor subtype.

14. A pharmaceutical composition for the treatment of erectile
15 dysfunction which comprises a pharmaceutically acceptable carrier, a therapeutically effective amount of an agonist of the melanocortin receptor and a therapeutically effective amount of a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist.

20 15. The pharmaceutical composition of Claim 14 wherein the inhibitor of the cyclic-GMP-specific phosphodiesterase is an inhibitor of the type V phosphodiesterase (PDE-V) isozyme and the alpha-adrenergic receptor antagonist is selective for the alpha-2 receptor subtype.

25 16. The pharmaceutical composition of Claim 15 wherein the alpha-2 receptor antagonist is MK-912.

17. The pharmaceutical composition of Claim 15 wherein the PDE-V inhibitor is selected from the group consisting of:

- 30 a) sildenafil citrate,
b) IC-351,
c) M-54018,
d) M-54033, and
e) E-4010.

18. The pharmaceutical composition of Claim 17 wherein the PDE-V inhibitor is sildenafil citrate.

5 19. The pharmaceutical composition of Claim 14 wherein the agonist of the melanocortin receptor is selective for the melanocortin-4 receptor (MC-4R) subtype.

10 20. The use of an agonist of the melanocortin receptor in combination with a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist for the preparation of a medicament useful to treat erectile dysfunction.

15 21. The use of Claim 20 wherein the inhibitor of the cyclic-GMP-specific phosphodiesterase is an inhibitor of the type V phosphodiesterase (PDE-V) isozyme.

22. The use of Claim 21 wherein the inhibitor of the type V phosphodiesterase isozyme is sildenafil citrate.

20 23. The use of Claim 20 wherein the alpha-adrenergic receptor antagonist is MK-912.

25 24. The use of Claim 20 wherein the agonist of the melanocortin receptor is selective for the melanocortin-4 receptor (MC-4R) subtype.

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(54) Title: METHODS AND COMPOSITIONS FOR TREATING ERECTILE DYSFUNCTION

(57) Abstract: The present invention provides for a method for the treatment of erectile dysfunction in a male or female human subject in need of such treatment comprising administration of a therapeutically effective amount of an agonist of the melanocortin receptor in combination with a therapeutically effective amount of a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist. Further, the present invention provides for pharmaceutical compositions useful in the methods of the present invention, as well as a method of manufacture of a medicament useful for treating erectile dysfunction.

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WEST CAS/STN WPIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	WO 99/30697 A2 (PFIZER PRODUCTS INC.) 24 June 1999 (24.06.99), see entire document (kit of sildenafil and E.G. Yohimbine).	1-24
Y, P	WO 99/59584 A1 (SCHERING CORPORATION) 25 November 1999 (25.11.99), see entire document (kit of sildenafil, Yohimbine, Phentocamine, etc.).	1-24
Y, P	WO 99/60985 A2 (SAINT LOUIS UNIVERSITY) 02 December 1999 (02.12.99), see entire document (mixture of Yohimbine, phentolamine, papaverine).	1-24

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	WO 99/30718 A2 (SCOTT) 24 June 1999 (24.06.99), see entire document (impotence combination of prostaglandins, anaesthetics instead of "VIAGRA" (SILDENAFIL).	1-24
Y	WO 96/16657 A1 (PFIZER LIMITED) 06 June 1996 (06.06.96), see entire document (sildenafil-like pyrazo pyrimidinones, or alternatively, erectile dysfunction combinations of papaverine, phentolamine and prostaglandins).	1-24
Y	US 6,037,346 A (DOHERTY, JR. et al.) 14 March 2000 (14.03.00), see entire document (kit of sildenafil and yohimbines).	1-24
Y, P	US 6,007,824 A (DUCKETT et al.) 28 December 1999 (28.12.99), see entire document ("VIAGRA" or synergistic natural sexual dysfunction agent combinations).	1-24
Y, P	US 5,994,294 A (GARVEY et al.) 30 November 1999 (30.11.99), see entire document (erectile dysfunction combination of yohimbine and phentolamines).	1-24
Y, P	US 5,962,528 A (SCOTT) 05 October 1999 (05.10.99), see entire document (impotence treating combination of prostaglandins).	1-24
Y, P	US 5,932,538 A (GARVEY et al.) 03 August 1999 (03.08.99), see entire document (erectile combination of yohimbine and pitewtolamine).	1-24
Y	US 5,731,339 A (LOWREY) 24 March 1998 (24.03.98), see entire document (impotence combination of yohimbine and phentolamine).	1-24
Y	US 5,567,706 A (GAVRAS) 22 October 1996 (22.10.96), see entire document (combination of yohimbine and known impotence adrenoceptor agents).	1-24
Y	US 5,576,290 A (HADLEY) 19 November 1996 (19.11.96), see entire document.	1-24
Y, E	US 6,051,555 A (HADLEY) 18 April 2000 (18.04.00), see entire document.	1-24

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 94/28902 A1 (PFIZER LIMITED) 22 December 1994 (22.12.94), see entire document.	1-24
Y, P	WO 99/66933 A1 (NEW MILLENNIUM PHARMACEUTICALS RESEARCH, INC.) 29 December 1999 (29.12.99), see entire document.	1-24
Y, P	EP 0 960 621 A2 (PFIZER INC.) 01 December 1999 (01.12.99), see entire document.	1-24
Y, P	WO 97/03675 A1 (LABORATOIRE GLAXO WELLCOME S.A.) 06 February 1997 (06.02.97), see entire document.	1-24